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POST – COVID SYNDROME. REVIEW

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Abstract

Introduction: Coronaviruses are important pathogens of humans and animals. At the end of 2019, a new coronavirus was identified as the cause of a group of pneumonia cases in Wuhan, a city in the Chinese province of Hubei. It spread rapidly, leading to an epidemic throughout China, followed by a global pandemic.

Objective: to analyze and systematize publications devoted to the study of clinical and laboratory markers of post-COVID syndrome.

Search strategy: literature search was carried out in the electronic databases PubMed, The Cochrane library, Google Scholar and e-library by keywords (COVID-19, markers of post-COVID syndrome, variants of SARS-CoV-2, long-term manifestations of COVID-19, post-COVID complications). Relevant papers reflecting the characteristics of the problem were accepted for description in the review.

Results: Long-term manifestations of COVID-19 include lesions from the respiratory, cardiovascular, renal, endocrine, reproductive, central nervous system, gastrointestinal tract and liver, as well as inflammatory, autoimmune and rheumatological complications, chronic pain, chronic fatigue. Psychiatric/emotional health and well-being suffers, which leads to a deterioration in the quality of life of patients.

Conclusions: It is extremely important to determine which patients are at risk and which will require long-term follow-up. There is a great need for strategies regarding screening processes, resource provision, approved care pathways, and multidisciplinary rehabilitation services.

***Keywords**: COVID-19, markers of post-COVID syndrome, variants of SARS-CoV-2, long-term manifestations of COVID-19, post-COVID complications.*

Резюме

ПОСТКОВИДНЫЙ СИНДРОМ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Коронавирусы являются важными патогенами человека и животных. В конце 2019 года новый коронавирус был идентифицирован, как причина группы случаев пневмонии в Ухане, городе в китайской провинции Хубэй. Он быстро распространился, что привело к эпидемии по всему Китаю, за которой последовала глобальная пандемия.

Цель: проанализировать и систематизировать публикации, посвященные вопросам изучения клинико-лабораторных маркеров постковидного синдрома.

Стратегия поиска: поиск литературы был осуществлен в электронных базах PubMed, The Cochrane library, Google Scholar и e-library по ключевым словам (COVID-19, маркеры постковидного синдрома, варианты SARS-CoV-2, длительные проявления COVID-19, постковидные осложнения). Релевантные работы, отражающие характеристики проблемы были приняты для описания в обзоре.

Результаты: Длительные проявления COVID-19 включают поражения со стороны дыхательной, сердечно-сосудистой, почечной, эндокринной, репродуктивной, центральной нервной системы, желудочно-кишечного тракта и печени, а также воспалительные, аутоиммунные и ревматологические осложнения, хроническую боль, хроническую

усталость. Психиатрическое/эмоциональное здоровье и благополучие страдает, что приводит к ухудшению качества жизни пациентов.

Выводы: Крайне важно определить, какие пациенты находятся в группе риска, а какие потребуют длительного наблюдения. Существует большая потребность в стратегиях в отношении процессов скрининга, предоставления ресурсов, утвержденных путей оказания помощи и многопрофильных реабилитационных услуг.

Ключевые слова: *COVID-19, маркеры постковидного синдрома, варианты SARS-CoV-2, длительные проявления COVID-19, постковидные осложнения.*

Түйіндеме

КОВИДТЕН КЕЙІНГІ СИНДРОМ. ӘДЕБИЕТТЕРГЕ ШОЛУ

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Кіріспе: Коронавирус адам мен жануарлар үшін басты қоздырғыш болып табылады. 2019 жылдың соңында коронавирустың жаңа түрі табылып, Қытайдың Хубэй провинциясының Ухань қаласында пневмония жағдайларының себебі ретінде анықталды.Ол тез арада таралып, бүкіл Қытайды эпидемияға, кейін жахандық пандемияға әкелді.

Мақсаты: постковид синдромының клиникалық және зертханалық маркерлерін зерттеуге арналған басылымдарды талдау және жүйелеу.

Іздеу стратегиясы: әдебиеттерді іздеу PubMed, the Cochrane library, Google Scholar және e-library электронды базаларында түйін сөздер бойынша жүзеге асырылды (COVID-19, ковидтен кейінгі синдром маркерлары, SARS-CoV-2 нұсқалары, COVID-19 ұзақ көріністері, ковидтен кейінгі асқынулар). Шолуда сипаттау үшін мәселенің сипаттамаларын көрсететін релевантты жұмыстар қабылданды.

Нәтижелері: COVID-19 ұзақ мерзімді көріністеріне тыныс алу, жүрек-қан тамырлары, бүйрек, эндокриндік, репродуктивті, орталық жүйке жүйесінің, асқазан-ішек жолдары мен бауырдың зақымдануы, сонымен қатар қабыну, аутоиммунды және ревматологиялық асқынулар, созылмалы ауырсыну, созылмалы шаршау жатады. Психиатриялық / эмоционалды денсаулық пен әл-ауқат зардап шегеді, бұл науқастардың өмір сапасының нашарлауына әкеледі

Қорытынды: Науқастардың қандай тобына қауіп төніп тұрғанын және қайсысы ұзақ бақылауды қажет ететінін анықтау өте маңызды. Скринингтік үрдістерге, ресурстармен қамтамасыз етуге, бекітілген көмек көрсету жолдарына және көпсалалы оңалту қызметтеріне қатысты стратегияларға үлкен қажеттілік бар.

Түйін сөздер: *COVID-19, ковидтен кейінгі синдром маркерлары, SARS-CoV-2 нұсқалары, COVID-19 ұзақ көріністері, ковидтен кейінгі асқынулар.*

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Introduction

Coronaviruses are important human and animal pathogens. At the end of 2019, a new coronavirus was identified as the cause of pneumonia in Wuhan, a city in Hubei province. It spread rapidly, followed by an epidemic throughout China, resulting in a global pandemic. In August 2020, the World Health Organization (WHO) designated COVID-19, which stands for Coronavirus Disease 2019 [70]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it was previously called 2019-nCoV.

Coronaviruses are enveloped positive-strand RNA viruses. Whole genome sequencing and phylogenetic analysis have shown that the coronavirus that causes COVID-19 is a beta-coronavirus of the same subgenus as severe acute respiratory syndrome (SARS) virus (as well as

several bat coronaviruses). The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has proposed designating the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[21].

The host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV, angiotensin-converting enzyme 2 (ACE2)[69]. SARS-CoV-2 binds to ACE2 through the receptor-binding domain of the spike protein. Cellular protease TMPRSS2 is also important for entry into SARS-CoV-2 cells [25].

Objective: to analyze and systematize publications on the study of clinical and laboratory markers of post-COVID syndrome.

Search strategy: Literature search was carried out in the electronic databases PubMed, The Cochrane library, Google Scholar and e-library using keywords (COVID-19, markers of post-COVID syndrome, SARS-CoV-2 variants, long-term manifestations of COVID-19, post-COVID complications). The search depth was 12 years; however, more distant indexing dates were taken to characterize the evolution of diagnostics. Relevant papers reflecting the characteristics of the problem were accepted for description in the review.

Sources were selected according to the underlying context of the study. Preference was given to publications in peer-reviewed journals. At the first stage, a general array of articles was selected, from which the most relevant ones were filtered by keywords and context.

Inclusion Criteria: reports on randomized and cohort studies conducted on large populations, full versions of articles, dissertations, diagnostic protocols in Russian and English with open access. The search for information was carried out by keywords.

Exclusion Criteria: articles, abstracts and scientific publications describing individual cases, summaries of reports, personal messages and abstracts. During the search, 76 sources were found.

Research results and discussion

Post-COVID-19 syndrome, Long COVID, post-acute sequelae of COVID-19, PASC, chronic COVID syndrome, CCS, long-haul COVID [9, 71]) — consequences of the novel coronavirus infection (COVID-19), in which up to 20% of people who have had a coronavirus infection suffer from long-term symptoms lasting up to 12 weeks and in 2.3% of cases longer [57, 72].

Postcovid syndrome is included in the International Classification of Diseases (ICD-10) [73], category code U09.9 Post-COVID-19 condition, unspecified, also including post-COVID condition [74].

Observational studies conducted among different populations (USA, Europe and Asia) have identified varying proportions of persistent symptoms following SARS-CoV-2 infection. Early studies have provided evidence of persistent COVID effects reporting short-term outcomes spanning the post-acute phase (4–12 weeks) of COVID-19 [3, 10, 13, 38, 47, 50, 51, 75, 76], larger cohorts with longer follow-up periods (over 12 weeks) illustrating the multisystem manifestations of so-called “long-term” or “chronic” COVID [20, 26, 63].

Eight retrospective and four prospective studies examined the post-acute and long-term effects of COVID in various populations with respect to ethnicity, inpatient/outpatient settings, disease severity (patients with mild, moderate, and severe COVID-19). Of these nine studies, the focus was on the post-acute phase, with a median follow-up of 32 days after discharge to 83 days (interquartile range 74–88) after hospitalization. Three studies provided data for 12 weeks with a mean follow-up ranging from 97 days (median, IQR 95–102) after discharge to 186 (IQR 175–199) after symptom onset.

The proportion of persistent symptoms varied significantly between studies. The highest proportion of post-acute COVID syndrome, 84.7%, was reported in an Italian study of 143 hospitalized patients, 20% of whom required non-invasive or invasive ventilation [51]. The most common symptoms were fatigue (53.1%), shortness of breath (43.4%), joint pain (27.3%), and chest pain (21.7%). A prospective UK study of 110 consecutive hospitalized patients reported a high proportion of persistent symptoms of 74% [3]. The most common symptoms were shortness of breath, excessive fatigue, and disability. The largest study reporting on post-acute COVID syndrome included 1409 patients admitted for home health care [76]. The most common symptoms included 42% pain, daily or constant, 84% shortness of breath with any exertion, 50% anxiety symptoms, and 47% confusion. Fatigue was the most common symptom reported in various studies, ranging from 30% to 72%, followed by shortness of breath, cough, confusion, memory loss, persistent pain, headache, joint pain (arthralgia), chest pain, anosmia, ageusia, palpitations, anxiety, depression, sleep problems, gastrointestinal symptoms, and hair loss.

In three studies (China and France), chronic or long-term COVID syndrome was reported: sleep problems - 23%, anxiety or depression - up to 29%, acute renal failure - in 13% of patients in the acute phase [26]. Another study including 538 patients (39% of them with critical or severe illness) showed that 49.6% of patients had at least one symptom during follow-up, with 28.3% reporting deterioration in physical condition or fatigue, 39% - difficulty breathing, 21.4% - shortness of breath, 14.1% - chest discomfort, 12.3% - pain, 7.1% - cough, 13% - cardiovascular complications, 23.6% - increased sweating and 18.6% alopecia [20].

Clearly, symptom reporting rates should be considered in terms of selection bias, as most of the studies were retrospective with small sample sizes and included hospitalized patients with varying severity of COVID-19. Future prospective population-based studies are needed to provide a reliable assessment of long-term COVID syndrome in the general population.

The lungs are the organ most likely to be seriously damaged by COVID-19 [1, 49]. Even in patients with mild symptoms, there may be lung involvement on computed tomography and persistent changes in lung function [15, 18, 23, 28, 49, 51, 56, 59, 63, 68]. Impaired lung function (restrictive disorders, reduced diffusing capacity, obstruction of small airways) were detected both early and later (2–12 weeks) after discharge [8, 19, 49, 56, 65, 66]. However, the most severe complication is pulmonary fibrosis (LF), and fibrotic changes are detected as early as 3 weeks after the onset of symptoms, regardless of the severity of the acute disease [28, 41, 42, 55, 60, 67]. LF has also been observed in severe illnesses caused by other coronaviruses (SARS

and Middle East respiratory syndrome) [32, 61]. Potential predictors of LF in COVID-19 include older age, severe disease, elevated D-dimer levels of lung disease, acute respiratory distress syndrome (ARDS), history of pulmonary or cardiovascular disease, prolonged mechanical ventilation, smoking, and chronic alcoholism.

There are several mechanisms that may be involved in acute and long-term injury after COVID-19, including injury associated with hypoxia and mechanical ventilation, tissue destruction due to uncontrolled release of cytokines and activation of the immune system, direct pneumocyte apoptosis due to ACE2 mediated viral invasion, surfactant inactivation, microvascular and thrombotic diseases, and endothelial dysfunction. An isolated decrease in diffusing capacity in a few patients also points to SARS-CoV-2-induced vascular injury; Pulmonary hypertension with or without evidence of thrombosis has been reported. Polymorphisms of ACE2, the entry receptor for SARS-COV-2, may also predispose to lung injury after COVID-19. Although persistence of the virus in lung tissue is not thought to be the cause, persistence of virus-infected syncytia-forming cells may play a significant role. SARS-CoV-2 induced proinflammatory and profibrotic cytokines [64] are overproduced during acute and subacute COVID-19, while the homeostatic mechanisms of lung repair are deregulated, leading to the development of LF; antiviral interferons impair lung recovery, further increasing disease severity [35].

Accumulating evidence indicates that cardiac complications associated with COVID-19 may occur or persist weeks or months after infection resolves [5]. Among COVID-19 survivors, 5-29% complain of chest pain, shortness of breath, or palpitations after recovery, even 6 months after acute infection [26]. Late cardiac magnetic resonance (MRI) findings suggestive of subacute myocarditis have also been reported in COVID-19 [27, 39, 40, 45, 53]. Although persistence of SARS-CoV-2 in myocardial tissue or myocardial inflammation after recovery may explain these findings, histological data are lacking. After 24–71 days, MRI studies suggest the presence of inflammation or scarring of the myocardium in 15–60% of patients, even in those who had no symptoms or only mild symptoms of acute illness. These results correlated with troponin levels [45] and inflammatory markers such as C-reactive protein, leukocyte count, and procalcitonin, suggesting a role for inflammation in myocardial tissue abnormalities [47].

Late cardiovascular complications have been found in 80% of children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Considering that other viral infections may exacerbate atherosclerotic events due to increased inflammatory and procoagulant load [46], these observations have led to the hypothesis that endothelial dysfunction may play a key role in the late cardiovascular complications of COVID-19, which is currently.

Despite the relative absence of studies investigating the long-term effects of SARS-CoV-2 on the cardiovascular system, existing evidence suggests an increased incidence of serious adverse cardiovascular events in recovered patients with COVID-19 after a median follow-up of 140 days [30]. In another study, consistent with previous data on subacute complications, myocardial injury was detected in 30% of patients at 3 months of follow-up after COVID-19 infection. In addition, postural orthostatic tachycardia syndrome has been observed in recovered patients experiencing significant disability even 6–8 months after acute infection [4].

There is cumulative evidence that COVID-19 affects brain function and may exacerbate the course of neurodegenerative and neuroimmune processes or neurological manifestations of systemic and non-specific inflammatory effects [17, 24]. Global CNS dysfunction due to microglia activation, persistent neuroinflammation, neuroimmunity dysregulation, and hippocampal atrophy is well known in critical conditions (eg, sepsis) [12, 29, 58]. Prolonged stay in the intensive care unit, mechanical ventilation, prolonged exposure to sedatives, sepsis, systemic inflammation, pre-existing cognitive dysfunction, neurological injury, and delirium increase the risk of cognitive decline and neurological complications after ARDS [48, 54]. Long-term consequences in patients with early neurological complications such as encephalitis or stroke on the background of acute COVID-19 can lead to serious complications - lifelong disability requiring long-term rehabilitation [17, 22, 43]. In addition, immunomodulatory drugs, such as corticosteroids, used in the acute phase of COVID-19 often have CNS side effects, including cognitive and sleep disturbances, delirium, and psychiatric manifestations, although symptoms disappear after taking the drug [58]. The most common self-reported neurological symptoms following COVID-19 include headache, vertigo, dizziness, anosmia, ageusia, hypogeusia, dysgeusia, insomnia, memory impairment, and decreased ability to concentrate (“brain fog”). Less common late manifestations include ischemic stroke, intracranial hemorrhage, encephalitis, encephalopathy, seizures, peripheral neuropathies, and autoimmune acute demyelinating encephalomyelitis. CNS involvement is not specific to SARS-CoV-2, as several post-acute and prolonged neurological manifestations have been reported during pandemics of influenza and other coronaviruses (SARS, MERS). Direct neuroinvasion, neuronal damage secondary to tissue hypoxia or inflammation, local dysregulation of the cytokine network, and disruption of the integrity of the blood-brain barrier with subsequent transmigration of infected immune cells have been postulated as pathophysiological mechanisms underlying long-term neurological consequences after coronavirus infections [37, 62].

A retrospective cohort study of 236,379 US patients found that the estimated incidence of neurological or psychiatric diagnoses over the next 6 months after COVID-19 was approximately 33%, with 12% of patients newly diagnosed with neurological or psychiatric disorders. The estimated incidence was even higher, approximately 46%, in critically ill patients admitted to the intensive care unit. Interestingly, most diagnostic categories were more common in COVID-19 patients compared to influenza patients (prone to microthrombi and cerebral structural changes in the hippocampus, islets, and partial white matter) [34, 37, 43]. Not surprisingly, older patients are more prone to long-term neurocognitive complications. Parkinsonism-like symptomatology has been reported as a

late onset of influenza, SARS, and recently post-COVID-19 in elderly patients (probably due to a-synuclein accumulation and autoimmune cross-reaction caused by viral infections) [6, 11, 14]. There is concern that COVID-19 may provoke a new wave of neurodegenerative diseases in susceptible patients [43]. Whether COVID-19 predisposes to worsening of pre-existing chronic neurodegenerative brain conditions, or whether chronic consequences of COVID-19 are more common in these patients deserves further investigation [11, 37, 43].

In addition, isolated chronic central nerve dysfunction (SARS-CoV-2 can enter the CNS via the olfactory nerve), such as anosmia, dysgeusia, or ageusia, common early symptoms of acute COVID-19, may persist long after acute infection [12, 31, 33, 34], this is associated with higher bilateral volumes of gray matter in the olfactory cortex [34].

Diabetes mellitus (DM) is a well-known risk factor for severe acute COVID-19. SARS-CoV-2 induces a pro-inflammatory state [16], and cytokine storm is more common in diabetic patients [2], leading to pancreatic damage and hyperglycemia [2], which can be exacerbated by corticosteroids. Long-term follow-up is needed to assess late-onset DM in patients without such a history who develop hyperglycemia during the acute phase of COVID-19. The hidden effects of SARS-CoV-2 in the adrenal, thyroid/parathyroid, and pituitary glands are not well understood. Cases of subacute thyroiditis and the emergence of autoimmune diseases, including Graves' disease and Hashimoto's thyroiditis, have been reported following COVID-19 [7, 36]. Home isolation during self-isolation can lead to low levels of vitamin D and impair immunity. Several patients have had abnormally low vitamin D levels and elevated parathyroid hormone levels 8 weeks after onset of COVID-19, which may also have a clinically significant impact on bone health [44, 52].

Conclusion.

It is critical to determine which patients are at risk and which will require long-term follow-up for long-term COVID-19. There is a great need for strategies around screening processes, resource provision, approved pathways of care and multidisciplinary rehabilitation services.

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